REMARKS

Claims 236, 238-251, and 257-308 are now pending in the application. Claims 242, 259 and 275-306 have been withdrawn. Claim 237 was previously cancelled and Claims 252- 256 are cancelled herein. Claims 236, 238-240, 243, 245, 249-251, 257, 258 and 260-267 are presently amended to improve clarity and to overcome the 35 U.S.C. §112 rejections in the present Office Action. Claims 307 and 308 are drawn to the methods of infecting the transgenic plant or transgenic plant cell comprising the DNA molecule as recited in step (d) of the amended Claim 236. Support can be found throughout the specification, in particular in the original claim 256 and at paragraph [0061] of the original specification. Support for the present claim amendments can be found throughout the specification as originally filed and no new matter is being added. The Examiner is respectfully requested to reconsider and withdraw the rejections in view of the amendments and remarks contained herein.

SPECIFICATION

The Specification was amended to recite that the orientation of the template stand of the double stranded DNA molecule read from the 3' to 5' orientation a DNA sequence comprising a promoter, a coding sequence for a heterologous polypeptide, a coding sequence to an IRES, and a DNA sequence corresponding to a complementary sequence to the coding sequence of a 3'UTR of a positive strand single-stranded RNA virus. This amendment to the specification clarifies that the template strand is used by the cell transfected with the DNA molecule to create the recombinant RNA transcript. Support for the amendment to the specification can be found in Figure 6 as originally filed.

CLAIM OBJECTION

Claim 236 is objected to for missing the recitation "and" after part ii) and before part iii). Applicant respectfully traverses the present rejection. Applicant has amended Claim 236 as recommended by the Examiner. This rejection has been rendered moot.

REJECTION UNDER 35 U.S.C. § 112

Claims 236, 238-241, 243-258, 262-263, and 266-267 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claim 236 has been rejected for allegedly having a last step which is inconsistent with the preamble of the claim, namely, a method for producing a heterologous polypeptide. Applicant has amended Claim 236 and have included step "e) translating the translatable mRNA in the transgenic plant or transgenic plant cell to form the heterologous polypeptide." This step is consistent with the preamble. Applicant respectfully requests reconsideration and withdrawal of the present rejection.

Claim 239 and 262 are alleged to lack antecedent basis for the limitation "the eukaryotic constitutive promoter." Applicant has amended Claims 236 and 260 and has inserted the limitation "a plant promoter" thereby making the antecedent basis proper in the dependent Claims 238, 239, 261 and 262, rendering this rejection moot. Applicant respectfully requests reconsideration and withdrawal of the present rejection.

Claims 240 and 263 are alleged to be unclear for reciting "heterologous polypeptide" in line 2. Applicant notes that Claim 236 recites "a sequence complementary to a coding sequence for a heterologous polypeptide". Hence, claim 240 refers to the coding sequence and the heterologous polypeptide of Claim 236 and provides proper antecedent basis back to Claim 236. The same rationale is applied as to Claim 263 which recites the coding sequence and the heterologous polypeptide of Claim 260. Applicant has amended Claims 240 and 263 to obviate the present antecedent basis rejection. Applicant respectfully requests reconsideration and withdrawal of the present rejection.

Claims 243 and 266 are alleged to be unclear for reciting "the 3'UTR of a first positive strand single-stranded RNA plant virus is a 3' UTR of a first positive strand single-stranded RNA plant virus having no DNA stage." Applicant has amended Claims 243 and 266 to remove reference to a "first positive strand single-stranded RNA plant virus" and included the language suggested by the Examiner to refer to the RNA as being a positive strand single-stranded RNA with no DNA stage. Applicant further respectfully submits that the phrase a "3' UTR of a first positive strand single-stranded RNA plant virus having no DNA stage" is not unclear. It specifically recites a genus of plant RNA viruses in which the virus has a genomic structure encoding a single stranded RNA that is a "sense" strand operable to be translated in the host cell. The positive strand single-stranded RNA viruses possess genetic information that consists of a single strand of RNA that is the positive (or sense) strand which encodes mRNA (messenger RNA). Replication in positive-strand RNA viruses is via a negative-strand RNA intermediate,

but does not produce a DNA transcript in any step because such viruses use RNA dependent RNA polymerases and therefore do not require DNA to produce the minus RNA strand for transcription and/or translation. Furthermore, the specification on pages 25-26 provides examples of positive single-stranded RNA 3'UTRs from positive strand single-stranded RNA plant viruses that do not have a DNA stage in their replication and infectious processes. A second, positive strand single- stranded RNA virus can be any positive strand single-stranded RNA virus that recognizes the 3'UTR encoded by the recombinant RNA transcript. The specification describes which viruses may fall into that category, including the same viruses used to initially obtain the 3'UTR in the recombinant RNA transcript or different but closely related viruses that recognize the 3'UTR initially used to construct the recombinant RNA transcript. (See specification at page 11, paragraph [0030], lines 25-29.) Once the infecting virus recognizes the 3'UTRs of the RNA transcript, the 3'UTR serves as an initiation site for the virus specific RNA dependent RNA polymerase (RdRP). The RdRP is then able to form a complementary strand of the RNA transcript which results in a translatable mRNA for protein synthesis in the host cell. Methods for determining whether a positive strand single-stranded RNA virus can recognize and utilize a different 3'UTR are exemplified in the specification, using for example, the methods described in Teycheyney et al. (See specification at page 11, paragraph [0030].) Applicant respectfully requests reconsideration and withdrawal of the present rejection.

Claim 245 is alleged to lack antecedent basis for the term "said DNA molecule." Applicant has amended Claim 245 to recite "DNA sequence" which is clearly recited in

Claim 236 from which Claim 245 depends. As such, the present amendment renders this rejection moot. Applicant respectfully requests reconsideration and withdrawal of the present rejection.

Claims 253 and 254 are alleged to be indefinite because the phrase "the cDNA of a second positive strand single-stranded RNA plant virus" is unclear. Applicant has explained what a "second positive strand single-stranded RNA plant virus" means in context of the teachings of the specification, and is therefore not believed to be unclear. However, in an attempt to expedite prosecution and without acquiescing to the present rejection, the Applicant has cancelled Claims 253 and 254 thereby rendering this rejection moot.

Claim 257 is alleged to lack antecedent basis for the term "the RNA comprising at least one sequence encoding a polypeptide component of an RNA virus replication complex." Applicant has amended Claim 257 to recite, "The method of producing a heterologous polypeptide of claim 236, wherein the plant virus comprises an RNA comprising a sequence encoding an RNA-dependent RNA polymerase operable to transcribe the RNA transcript produced by the transgenic plant or the transgenic plant cell having a RNA sequence comprising in the 5' to 3' direction a complementary RNA copy of the DNA sequence." As such, the present amendment renders this rejection moot. Applicant respectfully requests reconsideration and withdrawal of the present rejection.

Claim 258 is alleged to lack antecedent basis for the term "the molar concentration ratio of heterologous polypeptide in a cell." Applicant has amended Claim 257 to recite, "The method of producing a heterologous polypeptide of claim 236, wherein the heterologous polypeptide produced in a cell infected with the RNA nucleic acid when compared as a molar ratio to the amount of the heterologous polypeptide produced in a cell not provided the RNA nucleic acid, ranges at least from about 50:1 to about 10,000:1." Applicant has removed reference to "the molar concentration ratio of heterologous polypeptide in a cell." Applicant respectfully requests reconsideration and withdrawal of the present rejection.

Claim 267 is alleged to be indefinite because the phrase "the 3'UTR of a positive strand single-stranded RNA plant virus" is unclear. Applicant respectfully submits that the genus of plant viruses that belong to the class of viruses that replicate via positive strand single-stranded genomes encoding RNA-dependent RNA polymerases are well known. The specification is replete with examples of such 3'UTRs from this class of plant viruses. (See specification at pages 25-29). The 3'UTR contains the recognition and initiation site for synthesis of a complementary strand by the viral replication complex. Applicant respectfully submits that one of ordinary skill in the art at the time of the filing of the application would have been fully aware and have understood the meaning of the phrase "3'UTR of a positive strand single-stranded RNA plant virus." Nevertheless, without acquiescing to the present rejection, Claim 267 has been amended to recite, "...the positive strand single-stranded RNA virus RNA having no DNA stage is

a 3' UTR of a bromovirus." Applicant respectfully requests reconsideration and withdrawal of the present rejection.

Claims 236, 238-241, 243-258 and 260-274 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claims are alleged to contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is respectfully traversed.

The Office Action alleges that the specification fails to describe the conserved structure of the 3'UTRs and their corresponding stimuli. In support of this allegation, the Office Action notes that the specification teaches the replication complex of BMV could recognize and synthesize a complementary copy of a CCMV transgene that contains a complete 3'UTR.

Applicant respectfully submits that the 3' UTR of positive strand single-stranded RNA viruses were adequately exemplified in the specification as originally filed, providing no less than three hundred and fifty examples of 3'UTR from positive strand single stranded RNA viruses, the majority being plant positive strand single-stranded RNA viruses. DNA and RNA examples of such 3' UTR sequences were provided in the specification as originally filed as shown in paragraphs [0055]-[0058]. Applicant has also amended Claim 236 to recite that the infecting RNA nucleic acid is operable to recognize the viral RNA replication initiation site present in the RNA transcript and convert the RNA transcript into a translatable mRNA. One of ordinary skill in the art

having knowledge of plant virus replication in the field would have known by reading the specification that the recognition of viral 3'UTR, including the viral RNA replication initiation site, is restricted to the same viral species or phylogenetically closely related strains. One of ordinary skill in the art could have easily determined which of the exemplified species of plant viruses were operable to recognize the 3' UTR as indicated in paragraphs [0055]-[0058] using the methods of Teycheyney et al. specifically noted in the specification as filed on page 11, paragraph [0030].

Furthermore, several of the plant viral 3'UTRs were described in the nucleotide databases from which polynucleotide sequences could have revealed commonly encoded transcription factors, initiation sites and other nucleic acid sequences that encode structural attributes that are necessary for recognition of the 3'UTR and activation of the plant cell's transcription machinery to produce a functional mRNA. These commonly encoded features, including tRNA-like elements, polyA tails and non-tRNA heteropolymeric termini, were previously known to those of skill prior to the time of filing the present application.

The categories of 3'UTR structures utilized by particular plant viruses were known at the time of filing. In the exemplified embodiments of the present application, the 3'UTR used in the DNA sequence encoding an RNA viral replication initiation site could be tailored for use with either the same strain of viruses or a phylogenetically related virus that use the same 3' termini structure illustrated above and discussed in Dreher, T.W., (1999) "Functions of the 3'-Untranslated Regions of Positive Strand RNA Viral Genomes," Annu. Rev. Phytopathol., 37:151-174 at pages 151-158. (A courtesy copy is provided herewith). Whether an initial 3'UTR used in the DNA sequence would

have been recognized and activated by a later RNA nucleic acid is a matter of routine experimentation using methods described by Teycheyney et al. specifically noted in the specification as filed on page 11, paragraph [0030]. Teycheyney teaches methods, for determining whether a 3'UTR from a first positive strand single-stranded RNA virus is operable to recognize a different viral RNA replication initiation site and convert the RNA transcript produced by the first 3'UTR to a translatable mRNA using routine experimentation. The methods of Teycheyney can be used to verify if a first 3' UTR sequence (viral RNA) from a positive strand single stranded RNA virus having a sequence encoding a viral RNA replication initiation site can serve as a template for synthesizing a complementary strand using the same or different viral 3'UTR introduced into a transgenic plant or a transgenic plant cell.

Applicant respectfully submits that those of skill in the art have a high level of skill. The number of species required to form the representative number varies inversely with the level of skill in the art, therefore, those of ordinary skill in the art of viral RNA replication and mRNA expression would have concluded that the Applicant was in possession of the entire breadth of the claimed genus of combinations of 3'UTR and RNA nucleic acids that comprise a 3'UTR operable to activate and initiate the viral replication site for effective transcription/replication of the minus strand of the RNA transcript into translatable mRNA.

Accordingly, Applicant respectfully requests reconsideration and withdrawal of the present rejection.

Claims 236, 238-241, 243-258 and 260-274 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. This rejection is respectfully traversed.

The Office Action alleges that the specification does not enable a method for producing a heterologous polypeptide by using any promoter, any 3' UTR from any positive strand single-stranded RNA virus or by providing any stimulus for synthesis of an RNA complementary to any RNA transcript of the recombinant DNA. In support of this allegation, the Office Action notes that the specification only teaches the example of using the replication complex of BMV which could recognize and synthesize a complementary copy of a CCMV transgene that contains a complete 3'UTR.

Applicant has discussed above the amendment to Claim 236. For the reasons set forth above in regard to the written description rejection, Applicant respectfully submits that the claims as amended are enabled by the specification as of the application filing date.

Claim 236 now requires a step of infecting the transgenic plant or the transgenic plant cell with an RNA nucleic acid operable to recognize the viral RNA replication initiation site on the RNA transcript and convert the RNA transcript produced by the transgenic plant or transgenic plant cell to a translatable mRNA. The specification exemplifies RNA viruses which can be used to infect the transgenic the plant or plant cell to provide the infectious RNA nucleic acid encoding a RNA dependent RNA polymerase operable to recognize the RNA replication initiation site present on the RNA transcript. The initial 3'UTR used in the DNA molecule can be the same or different as the 3'UTR found in the infecting RNA nucleic acid (for example, a positive strand single-stranded

RNA virus having no DNA stage) (See specification at page 39, paragraph [0063].) In fact, the specification teaches which combinations cannot be used together, for example, the infecting RNA nucleic acid cannot be derived from Cucumber mosaic virus when the 3' UTR of the recombinant RNA transcript is that of Lettuce mosaic virus.

Regarding the assertion that the specification fails to reduce the invention to practice, the Examiner is respectfully reminded that an Applicant need not have actually reduced the invention to practice prior to filing. (See MPEP §2164.02). Regarding the three points of non-enablement discussed in the Office Action at page 10, the Applicant will address each one in the order that they are presented.

First, in regard to the use of a promoter, the Applicant has amended the claims to recite the use of a plant promoter, making this aspect of the rejection moot.

Second, the Office Action asserts that the RNA transcript of the recombinant DNA construct needs to encompass the three parts of the DNA sequence including a heterologous polypeptide, an IRES and a 3'UTR (Office Action at page 10, lines 8-11). Applicant respectfully submits that Claims 236 and claims dependent thereon already provided for an RNA transcript that included the three DNA parts referred to in the Office Action at page 10 and were therefore enabled in regard to the Examiner's second point. None of the RNA transcripts recited in Claim 236 would be produced lacking the 3 parts of the DNA sequence including the coding sequence for a heterologous polypeptide, an IRES and a 3'UTR. To make this statement more accurate, Applicant respectfully submits that in order to produce a mRNA which is translatable by the infected transgenic plant or transgenic plant cell, the DNA must encode a promoter operable to be used in plant cells, a sequence complementary to the coding sequence for a

heterologous polypeptide, a sequence complementary to a plant virus IRES, and a 3' UTR sequence having a sequence encoding a viral RNA replication initiation site.

Third, the Office Action asserts that the specification fails to provide guidance on how to obtain 3'UTR (sic) from any unexemplified positive single-stranded virus that can be stimulated by any unexemplified means to synthesize the RNA complementary to the RNA transcription of the DNA sequence. This characterization is plainly not supported by the specification. Applicant respectfully submits that there are over three hundred examples of 3' UTRs from single strand positive-stranded RNA viruses, at least half of them being plant viruses. Furthermore, the specification exemplifies combinations of 3'UTRs from one strain of virus capable of producing a RNA dependent RNA polymerase capable of reading and activating the a second (same or different) 3' UTR viral RNA replication initiation site encoded by the recombinant DNA and operable to convert the RNA transcript produced by the transgenic plant or the transgenic plant cell to a translatable mRNA. Contrary to the Office Action unsupported statement that the specification lacks any assay to perform the selection of 3'UTR because the stimulation is unspecified, the specification on page 11, paragraph [0030] states,

> The virus used to stimulate synthesis of the RNA complement of the recombinant RNA upon infection or transfection of viral nucleic acid can be identical to the virus used as the source of the 3' UTR of the transgene. The virus used to stimulate synthesis of the RNA complement of the recombinant RNA can also be different from the virus source of the 3' UTR, provided that the replication complex formed upon infection or transfection of the stimulating viral nucleic acid recognizes the 3' UTR of the recombinant RNA. Recognition of the 3' UTR of the recombinant RNA by an infecting or transfecting virus can be determined by standard methods known in the art (for example, the methods disclosed in Teycheney et al., *J. Gen. Virol.* 81: 1121-1126, 2000).

The state of the art combined with the guidance provided by the specification would have enabled those of skill to select a 3'UTR for inclusion into a DNA construct and an RNA nucleic acid that contained a RNA dependent RNA polymerase that recognizes or is operable to recognize the viral RNA replication initiation site present in the complementary RNA transcript of the recombinant DNA, and convert the complementary RNA transcript produced by the transgenic plant or the transgenic plant cell to a translatable mRNA. Since Claim 236 has been amended to recite infecting the transgenic plant or transgenic plant cell with an RNA nucleic acid operable to recognize the viral RNA replication initiation site, the Office Action's assertion that the method uses "3' UTR from any unexemplified positive single-stranded virus that can be stimulated by any unexemplified means to synthesize the RNA complementary to the RNA transcription of the DNA sequence" is now obviated. One of ordinary skill in the art would readily recognize that the specification provides several examples of 3'UTRs from plant viruses that can be used to provide a replication complex and RNA dependent RNA polymerase which upon infection or transfection is operable to recognize the 3' UTR of the recombinant RNA. Selection of the 3' UTR of the recombinant RNA by an infecting or transfecting virus, for example, was taught in the specification to be readily determined by standard methods known in the art without undue experimentation. (For example, the methods disclosed in Teycheney et al., *J. Gen. Virol.* 81: 1121-1126, 2000 at paragraph [0030]).

Accordingly, Applicant respectfully requests reconsideration and withdrawal of the present rejection.

CONCLUSION

Applicant submits that the claimed methods for producing a heterologous polypeptide are fully described and enabled commensurate with the full scope of the claimed subject matter. In particular, the claims have been amended to recite the enabled subject matter noted by the Examiner in the present Office Action in order to advance prosecution of this case. Practice of these methods does not require undue experimentation, beyond the level of selecting compatible 3'UTR sequences that are operable to recognize each other and provide RNA dependent RNA polymerase substrate specificity using the methods taught in the specification and standard experiments routine in the art. Accordingly, Applicant submits that the amended claims are fully described and enabled, and request withdrawal of the rejections under 35 U.S.C. §112.

Applicant submits that the amended claims are now in condition for allowance. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (248) 641-1600.

Respectfully submitted,

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